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EXAMINER	
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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/608,997	PROCKOP ET AL.	
	Examiner	Art Unit	
	ROBERT M. KELLY	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,18,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,18,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and argument of 3/14/08 are entered.

Claims 1 and 7 are amended.

Claims 1-7, 18, 21, and 22 are pending and considered.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant remains advised that should claim 1 be found allowable, claim 22 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof, for reasons of record. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 22, which depends from Claim 1, requires the administration to be performed by direct injection. However, Claim 1 requires the injection to be into the brain of the patient, which is necessarily direct injection into the brain. Hence, these claims, despite a slight difference in wording, are substantial duplicates.

Response to Argument – DP warning

Applicant's argument of 3/14/08 has been fully considered but is not found persuasive.

Applicant argues that Claim 22 is limited to use of a shunt or any other means known to the Artisan, and hence, injection to the brain may encompass more than just direct injection, as it may encompass using a shunt (p. 4, paragraph 3).

Such is not persuasive. First, the citation to page 22 is incorrect. The disclosure is on page 15 of the specification. Second, the broad claims includes such methods too, and hence, there is no difference achieved even if Applicant's argument is valid. Third, as the claim is dependent from the broad claim, it must necessarily include the more narrow embodiments. Fourth, as the direct injection includes "any other means known to a person skilled in the art", this again stresses the breadth to be the same.

Hence, the warning is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of the amendments, the rejections of Claims 1-7, 18, and 22 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps, are withdrawn.

To wit, the amendments now recite the step of predifferentiation and make clear what such step is prior to, in order to be pre-differentiated. Further, as the cells are now clearly

predifferentiated from bone marrow isolated cells, Claim 18 is clear with regard to immunological isolation.

Claim Rejections - 35 USC § 112 - Enablement

Claims 1-7, 18, and 21-22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record, and as rewritten below for a clear and concise record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Law

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope.

It is noted that any particular factor may outweigh all factors, and even extraneous factors may overwhelm the other factors to make it such that undue experimentation must be found. Undue experimentation is not one of the amount of experimentation required *per se* but due to the fact that such experimentation would be required to reasonably predict the working embodiments encompassed by the claimed invention.

Breadth of the Claims

The claims encompass providing isolated syngeneic stromal cells which are predifferentiated into astrocytes to the brain of a human suffering from any disease, disorder or condition of the central nervous system. The method steps encompass isolating bone marrow from the syngeneic patient, isolating stromal cells from said bone marrow, differentiating said stromal cells into astrocytes, and administering such stromal cells to the patient by injection into the brain of said patient in an amount of 10^5 to 10^{13} cells per 100 Kg patient.

It should be noted that these claims, drawn to "providing" are only found to encompass therapy of the disease, disorder, or condition, by such providing (e.g., SPECIFICATION, p. 5), and hence, the claims must be enabled for therapy of any disease, disorder, or condition of the central nervous system.

Claim 2 requires the donor to not be suffering from a disease, disorder, or condition of the central nervous system. Such claim necessarily requires that Claim 1 and the other dependent claims also encompass the donor to be suffering from the disease, disorder, or condition. Hence, as stated above, the Artisan would outweigh all the other factors with this fact to determine that such would not provide therapy, but would only add cells to the individual which would exacerbate the disease, disorder or condition, as the "therapeutic" cells have the same disease. Moreover, nothing in the other factors has been found to outweigh this fact, and hence, it is undue experimentation to find those embodiments which would be efficacious in therapy when using such equally-defective cells for therapy.

Claim 3 requires the donor to be human.

Claim 4 requires the disease, disorder or condition to be genetic disease, a tumor, trauma, or a stroke. Claims 5 and 6 further limit such to injury to the tissues/cells of the CNS or a brain tumor.

Claim 7 requires the administered atrocyte cells to remain or replicate in the CNS of the recipient.

Claim 18 requires the stromal cells to be immunologically isolated from the recipient by some barrier from interaction with the immune system of a patient.

Claim 21 requires the isolated stromal cells to be differentiated into astrocytes by co-culture *in vitro* with astrocytes, prior to administration to the patient.

Claim 22, as shown in the DP warning, above, is the same scope as Claim 1.

The Nature of the Invention and State of the Prior Art

Applicant's invention is in the nature of somatic cell therapy for disorders, diseases, and conditions of the central nervous system in humans.

With regard to somatic cell therapy, a number of problems exist with regard to the transplanting of enough cells and an effect for a long enough period of time to effect treatment. To wit, Bartley, et al. (2003) Expert Opin. Biol. Ther., 3(4): 541-49 provides an overview for stem cell therapy for cerebral palsy (TITLE) which will suffice to delineate some of the problems with such therapies. Bartley only recognizes that two methods of administration appear to be feasible for treatment of cerebral palsy, those of intravenous or direct injection (p. 542, col. 1, paragraph 4), neither of which (meaning that specifically even direct injection), as will be shown below, is yet to be reasonably predictive of delivering enough cells to the site of action. In stating such, Bartley also recognizes that it is not reasonably predictable that any therapy can be effected with such cells injected into the vasculature, due to the permeability of the blood-brain barrier (Id.). Hence, Bartley is recognizing that administration, even when direct, is not reasonably predictive of any particular treatment. Specifically, with palsy, as with many diseases of the central nervous systems, patients have differing effects with regard to amounts of grey or white matter (and specific cell types and ratios of cell types) being lost, and therefore, the type of cell used to effect such therapy must be able to reasonably predictably differentiate into each of the cell types in the correct proportions (p. 542, col. 1, paragraph 5), and, in fact, it is not even reasonably predictable which or whether both need to be replaced in any particular instance of the disorder (Id.). Therefore, even for any subset of diseases of the CNS, it is not reasonably predictable which cells to replace in the first place, much less whether

marrow stromal cells, or even astrocytes, can do so for each cell type and in the correct proportions. Moreover, mere replacement of certain forms of cells may not effect any particular disease, as in palsy, where Bartley demonstrates that it is not reasonably predictable that replacement of myelin, without replacement of the axons themselves, would facilitate any functional improvement (p. 542, col. 2, paragraph 2).

Bartley also indicates that the choice of cell type, stage of differentiation, and derivation of the cells is a critical issue, indicating the specific stem cell type (e.g., he is encompassing both astrocytes and stromal cells) may not be efficacious for any particular form of palsy, much less any disorder of the central nervous system (Id., paragraph 3). With regard to bone marrow stromal cells, Bartley recognizes that crude bone marrow can generate neural progenitor cells in culture and individuals at autopsy who had received bone marrow transplants have been shown to comprise neurons arising from the transplant (p. 543, col. 2, paragraph 4). (It is noted that Applicant's showing is that stromal cells of the bone marrow generate astrocytes when injected into the brain, and hence, the Artisan would be left to wonder why Bartley's use of stromal cells did not effect therapy.) However, such evidence does not enable Applicant's invention, because it is post-filing evidence, citing articles that are post-filing evidence, and these articles teach *in vitro* differentiation, and the patients had whole bone marrow transplants, not stromal cell implants. Still further, the simple presence of structure (the cells being present) does not reasonably predict functional replacement to affect therapy (e.g., Swallow, et al. (1999) Restorative Neurology and Neuroscience, 15(4): 297-303 demonstrates that although structure may form, the functional connections required may not be formed by the cells, even in the case of native cells of the CNS). Hence, simply adding a bone marrow stromal cell, even if it

differentiates into an astrocyte and further into the various cell types required to treat the disease, even if in the proportions required, the Artisan would not reasonably predict that the required functional connections are formed such that therapy would be affected in any particular disorder.

Still further, in some disorders the in many forms of disease/disorder/condition, the problem is not reasonably predicted to be solved by adding more cells in any form, but would require replacement of the existing cells to solve the problem. To wit, Keller, et al. (2000) Neuroscience, 98(1): 149-56 demonstrates that proteosome activity causes degeneration of aging spinal cord (whole article). The Artisan then would be left to figure out how other cells will cause these cells to repair their proteosome activity. Hence, again, in any specific form of disease, disorder, or condition, it is not reasonably predictable that therapy could be affected.

Bartley also provides numerous lines of evidence to indicate that marrow stromal cells can differentiate into various tissues and that such **may** be able to occur *in vivo* (p. 544, col. 1), but also there exists conflicting data (Id., paragraph 2), and hence, the Artisan would still not reasonably predict it to be efficacious in any specific embodiment even if it properly differentiated into the needed tissues and form the required connections with the CNS required. Further, Bartley questions the use of undifferentiated cells, and indicates that it is not reasonably predictable yet, requiring further experimentation, to determine the state of differentiation which should be applied in any particular treatment of any particular disease, disorder or condition (p. 544, last paragraph). Furthermore, it is noted that even when these cell differentiate in some fashion, it is not clear whether such is the source of the therapeutic effect, or whether recovery is mediated by some other substance elaborated by the implanted cells (p. 545, col. 1, paragraph 2), and therefore, even if the cells differentiate they may actually not cause any therapeutic effect at

all in any particular embodiment. Moreover, other results indicate that improvements in function may not be linked to the implantation of the cells themselves (Id., col. 2, paragraph 1), making the results suspect for any therapy associated with stromal cell therapy to the brain. Also, Bartley, even when a finding seems positive, indicates the need for further confirmation of the information before the data can be fully accepted (Id.).

In conclusion, Bartley indicates that while the data is encouraging, extensive experimentation is still required before human treatment will be feasible (p. 545, col. 2, paragraph 2; p. 546, col. 1). Clearly, Bartley is indicating that somatic cell therapy with stromal cells is not reasonably predictable of therapy in humans at this point, which is even after Applicant's filing date.

Hence, from reviewing Bartley, the Artisan would only be able to make one conclusion: somatic cell therapy with stromal cells is not reasonably predictable of therapy in humans. This is because it is not reasonably predictable that, in humans, even for the two most promising routes of administration, i.e., intravascular and direct administration, that enough cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that the cells, even if they form in the correct amounts will form the correct functional connections with the nervous system; it is not reasonably predictable that the replaced cells, even if forming the correct functional connections would correct an already present problem; it is not reasonably predictable that mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first

place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell transplantation; it is not reasonably predictable that differentiation is required in the first place; and it is not reasonably predictable that if the transplanted cells have the same disease, disorder or condition that therapy would be affected.

Savitz, et al. (2003) J. Cardiovasc. Nurs., 18(1): 57-61 further demonstrates that these bone marrow stromal cells are not yet reasonably predicted to treat human CNS diseases in another context: that of stroke recovery (TITLE). While focusing on neural progenitors and fetal stem cells, Savitz discusses the possible use of stromal cells as another "potential" graft source for the treatment of strokes (p. 59). In it, Savits comments on Li, demonstrating "intriguing therapeutic possibilities" through these preliminary results (p. 59, col. 2, paragraph 2). However, Savitz also concludes that "much work lies ahead" because it remains largely unknown to what extent the different stem or progenitor cells differentiate into neurons or other brain cells, echoing the seniments expressed in Bartley (p. 60, col. 1). Furthermore, it is unknown if any particular stem cell would yield the correct percentage of progeny needed to reconstruct specific brain regions, what factors within the brain will support or the viability of such grafts, and will they integrate safely (p. 60, paragraph bridging columns). Hence, as Savitz concludes "Answering these and many other questions will require **extensive investigation** in order to yield useful data from which to draw practical information" (Last sentence, emphasis added).

Therefore, Savitz, in discussing a different disease, stroke, also concludes that much more experimentation is needed to elucidate the various problems of such somatic cell therapy for brain disorders. Such is also clearly linked to the type of stem cell, whether it will differentiate properly, and whether enough cells will be present and have enough of an effect for a long

enough period of time to effect treatment, and/or whether the cells will actually integrate and replace the dysfunctional tissues of the brain.

Moreover, Horn, et al. (2004) Molec. Ther., 10(3): 417-431, demonstrates that the small animal studies, in which most experiments have been performed to date (e.g., rodents), even if they are efficacious of treating a particular disease, are not reasonably predictive of treatment in humans. Horn discusses the potential of hematopoietic stem cells, stating that the use of such in stem cell therapy has great promise for the future, but does not recognize any currently reasonably predictable treatment for such stem cells (p. 417, paragraph bridging). (It should be noted that while the Examiner acknowledges that the reference is drawn specifically to treating central nervous system disorders, the issues to be raised (below) extend to all forms of treatment by stem cell gene transfer, and not just the treatment of the hematopoeitic system or ex vivo gene therapy with such cells; and if Applicant wishes to take issue with any of these art-recognized problems, the Examiner requests a scientific explanation of why such issue is not pertinent to Applicant's claimed therapy.) Horn first demonstrates that in initial results, it was shown that mouse hematopoeitic stem cells could be genetically modified with a degree of efficiency predicted to be therapeutic for many human diseases; however, in later experiments it became apparent that such therapy did not work in humans (p. 417, col. 2, paragraph 2). Hence, it is not reasonably predictable that mouse systems of gene therapy in stem cells is not predictable of therapy in humans. Next, Horn discusses the fact that large animal models may be better models for therapy in humans, but that such experiments are very labor intensive (p. 418). Also, similar to Bartley's conclusions, the source and differentiation state of the stem cell is critical and is not yet predictive of treatment of any particular disease (pp. 424-425, paragraph bridging). Further,

while still not being considered reasonably predictable at this point, Horn emphasizes that large animals models are needed to be examined to determine therapy, and that the small animals used, as in Applicant's experiments (below), are definitely not reasonably predictive of therapy in humans (pp. 426-427), and that such is due to, for example, the different endocrine signals and distinct stem cell pathways which larger animals have, which are different between the larger primates and the smaller ones (p 425, col. 1).

Hence, from Horn we see that the use of stem cells, even when genetically modified to further more closely resemble the tissues required to be replaced, that therapy is generally not predicted when it is efficacious in animals. Moreover, while it may be argued that majority of Horn is drawn to ex vivo gene therapy, Horn is still recognizing the same problems with regard to the models, i.e., that the replacement therapy may be effective in a rodent, but not in a human. To wit, in every case, the cells are required to provide the functional connections with the system to replace the malfunctioning cells, and as such, whether or not it is provided by administration of cells alone, or a cell that secretes a protein, such functional connection, when formed in a rodent model does not reasonably predict treatment of humans.

Lastly, with regard to immunologically isolated, if such cells are immunologically isolated, the cells cannot interact with the cells of the immune system, and therefore, the Artisan would not reasonably predict these cells to interact with the other cells of the body, as the projections and such cannot be reached by the macrophages and other immune system cells which can move into the area, and further, therefore, could not interact with other cells in the vicinity. Hence, the cells could not become an integrated part of the tissue.

In reviewing the above references, it is clear that the artisan would find any particular stem cell therapy in humans not reasonably predictable because: it is not reasonably predictable that, in humans, even for the two most promising routes of administration, i.e., intravascular and direct administration, that enough cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell transplantation; it is not reasonably predictable that differentiation is required in the first place; it is not reasonably predictable that even if structural recovery is obtained that such will equate to functional recovery; it is not reasonably predictable that, given the data seen *in vitro* or *in vivo* in small animal models, therapy could be effected; and it is not reasonably predictable that immunologically isolated cells could interact with the tissues to which they are supposed to be part of, and effect therapy.

The Level of Predictability in the Art

Because of the art, as shown above, does not disclose any therapy of any central nervous system disorder in a human, the Artisan could not predict, in the absence of proof to the contrary, that such applications would efficacious in any therapeutic treatment.

Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of ordinary skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

The Direction and Guidance Provided By Applicant

Applicant's specification broadly discusses the treatment of neurological damage in many diseases and the potential for the use of stromal cells (pp. 1-5), a summary of the invention broadly tracking the claims (pp. 5-7), definitions (pp. 9-14), broad disclosure of stromal cells, where they are isolated from, and predictions of ability to treat disease (pp. 14-21), further broad discussion of such cells with transgenes (pp. 21-25), culturing conditions (pp. 25-26), and administration methods and more culturing conditions (pp. 26-33).

However, such broad description does not constitute the specific direction and guidance the Artisan would require to reasonably predict whether, in humans, even for the two most promising routes of administration, i.e., intravascular and direct administration, that enough cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell

transplantation; it is not reasonably predictable that differentiation is required in the first place; it is not reasonably predictable that immune reactions will not destroy the implanted cells before therapeutic effects are seen; it is not reasonably predictable that, given the data seen *in vitro* or *in vivo* in small animal models, therapy could be effected; and it is not reasonably predictable that immunologically isolated cells could interact with the tissues to which they are supposed to be part of, and effect therapy.

The Existence of Working Examples

Example 1 demonstrates that stromal cells may contribute to connective tissue differentiation. Example 2 demonstrates the conditions for culture and isolation of stromal cells. Example 4 demonstrates long-term expression of genes in such cells. Example 5 demonstrates expression of such genes in subcutaneous diffusion chambers. Example 7 demonstrates that after direct administration of the stromal cells into rat brains, such cells may be found in the brains of rats for many weeks after administration, and migrate into various portions of the brain. Example 8 demonstrates that in the presence of astrocytes, the stromal cells exhibit a single marker of early astrocyte differentiation: glial fibrillary acidic protein.

Such examples however fall far short of the knowledge produced in the art, as described by the two articles provided above. They do not reasonably predict any therapy in humans for reasons given in the art and nature of the invention: mouse models and xenotransplantation in small animals is not reasonably predictive of any therapy in humans, even when cells produce physiologically relevant levels of genes (above). Moreover, they do nothing to overcome the lack of reasonable predictability it is not reasonably predictable that, in humans, even for the two most promising routes of administration, i.e., intravascular and direct administration, that enough

cells will reach the site of action; it is not reasonably predictable that any particular stromal cell, at any particular state of differentiation, will be able to produce enough of the differentiated tissues, and do so in the correct proportions to effect therapy; it is not reasonably predictable that mere replacement of cells is predictive of therapy in any particular case of a disease; it is not reasonably predictable that any effects seen to date are reflective of cell differentiation in the first place; it is not reasonably predictable that any of the effects seen to date are reflective of the cell transplantation; it is not reasonably predictable that differentiation is required in the first place; it is not reasonably predictable that immune reactions will not destroy the implanted cells before therapeutic effects are seen; it is not reasonably predictable that, given the data seen *in vitro* or *in vivo* in small animal models, therapy could be effected; and it is not reasonably predictable that immunologically isolated cells could interact with the tissues to which they are supposed to be part of, and effect therapy.

Undue Experimentation

Due to the reasons given in the last paragraph, the Artisan would have to perform undue experimentation to treat any particular disease, through any particular form of administration of such stromal cells, at any particular level of differentiation, with or without any particular transgene and promoter and other regulatory elements, with or without immunological isolation, to treat any particular instance of any disorder/disease/condition, due to the lack of reasonable predictability.

Such experimentation is considered extensive and undue.

Conclusion

Applicant's claimed invention is considered non-enabled for its whole scope due to the requirement for undue experimentation to find any particular working embodiment.

Response to Argument - Enablement

Applicant's arguments of 3/14/08 have been fully considered but are not found persuasive.

Applicant argues that the enablement must be based on the same standard as a rejection under 101 (p. 6, paragraph 1).

Such is not persuasive. The rejection is under 112, first paragraph, and hence, looking for utility appears to incorrect here. The Examiner recommends that Applicant reread the cited case to determine what exactly is being conveyed, because Applicant does not face a rejection under 101. Specifically *In re Brana* states that the pharmacological compounds are enabled as the compounds were shown in tests outside the specification. However, in the instant case, the compounds are questioned by the Artisan as affecting therapy in a reasonably predictable fashion, and hence, it would undue experimentation to determine which embodiments are enabled.

Applicant argues that under utility, in vitro data correlating to the particular therapy is enough (p. 6, paragraph 2).

Such is not persuasive. Applicant does not face a rejection for lack of utility. Moreover, Applicant's pertainent evidentiary showing is simply the production of astrocytes in murine brains from injected MSCs (e.g., EXAMPLE 7). Such does not even correlate to *in vitro* therapy, much less *in vivo* cell therapy.

Applicant again argues utility as the standard (pp. 6-7, paragraph bridging).

Again, such is not persuasive for reasons given above.

Applicant argues that the evidentiary showing is higher for FDA than for patentability (p. 7, paragraph 2).

Such is not persuasive. The standards are distinct, and none is "higher" than the other. Applicant must in this case be enabled for therapy. As shown, Applicant is not enabled for therapy.

Applicant argues that the use of post-filing evidence is not allowed (p. 7, penultimate paragraph).

Such is not persuasive. The reason any reference is utilized is to demonstrate what the Artisan thought. In a science such as biology/biochemistry the Art is experimental, and the absence of evidence is generally considered to demonstrate a lack of enablement. In addition, the Art the Examiner has cited, while sometimes being post-filing, also demonstrates that even post-filing, where more evidence is provided, the Artisan simply does not find the invention enabled. Applicant's earliest guaranteed filing date is 3/28/96. Nothing existed at all about these therapies with astrocytes at that time. Does that mean that the Artisan would accept Applicant broad assertions? The Examiner argues no, the assertions would be treated with skepticism, which is borne out by the art cited, and the citations within that Art which cites art prior to the earliest filing date.

Applicant argues broadly that the Claims are drawn to "providing", that many uses are disclosed, and hence, the claims are enabled (pp. 8-9 paragraph bridging-p. 9, paragraph 2).

Such is not persuasive. Applicant's disclosure is solely directed to therapy, and hence, the claims must be enabled for therapy.

Applicant argues that the various art citations are not technically relevant, selectively quoted, and ignore success in animal models, as well as much of it being post-filing (p. 8, last paragraph).

Such is not persuasive. The Examiner has provided a fair analysis of the problems. The citations are not selectively quoted, and the successes are drawn to animal models, which also demonstrate the lack of predictability in humans. Hence, the analysis is proper.

Applicant argues that utility analysis requires Bartley to be ignored (p. 9, paragraph 1).

Such is not persuasive. This is not a utility argument.

Applicant argues that while Swallow does show that functional connections may be required in some therapies, it is not required for all therapies (pp. 9-10, paragraph bridging).

Such is not persuasive. Applicant has not described in their specification which diseases could be treated without functional connection and integration, and how to treat such diseases thusly. Hence, given that Applicant's disorder/disease/condition is not limited in any way, and given that the Art is all generally post-filing, there appears to have been a complete lack of knowledge of such in the Art. Hence, the broad description is simply not enough to overcome the lack of enablement rejection.

Applicant argues that they need not be enabled for every embodiment (p. 10, paragraph 2).

Such is not persuasive. The Artisan is left to wonder which embodiments are actually enabled. As such, the Artisan would have experiment on each embodiment to determine which ones would work. Such is undue experimentation, amounting to inventing the breadth of invention claimed by Applicant.

Applicant argues that Swada is more pertinent to treatments claimed herein, as it teaches that the transplant is a good predictor of behavior and survival in the human brain (pp. 10-11, paragraph bridging).

Such is not persuasive. First Swada is not supplied, and hence, it is not considered for its whole breadth. However, it appears that Swada teaches a specific disorder and the use of transgenes in the cells to treat it, which were made by way of transgenic animals. Such is necessarily distinct from any disorder, and Applicant's claims do not even require a transgene.

Applicant argues that Gage argues that the claims are enabled (pp. 11-12, paragraph bridging).

Such is not persuasive. From the mere tenor of the argument, it is apparent that Gage is discussing the potential to develop therapies in the future, and fails to demonstrate therapy.

Applicant cites several articles for demonstrating the Artisan to recognize therapy as reasonably predictable (p. 12, penultimate paragraph).

Such is not persuasive. Again, the references have not been supplied. Further, each of the cited references appear, from the Arguments, to demonstrate specific therapies, and not a general therapy for all types of disorders/conditions/diseases.

Applicant argues that at best, the experimentation required is routine, and hence, the claims are enabled (pp. 13-14).

Such is not persuasive. The analysis provided is insufficient given the lack of predictability shown in the Art.

Applicant argues that the examples demonstrate utility, and hence, the claims are enabled (pp. 14-15, paragraph bridging).

Such is not persuasive. Applicant does not face a utility rejection.

Applicant argues that they have provided reasonable evidentiary showing for a utility, and hence, the claims are enabled.

Again, no rejection for utility has been provided. The rejection is one of undue experimentation, which is found for the claims, and hence, the claims are not enabled.

Conclusion

No Claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT M. KELLY whose telephone number is (571)272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert M Kelly/
Examiner of Art Unit 1633